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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,604	ASHKENAZI, AVI, ET AL.	
	Examiner	Art Unit	
	Robert Landsman, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The appeal brief of 02 July 2007 has been received and considered. Upon further consideration, finality of the previous Office Action (mailed 30 Aug 2006) is *withdrawn* solely to clarify the issues for appeal, and to provide Applicant with an opportunity to respond accordingly.

1. Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

A. Claims 119-1261 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility.

Claims 119-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific, and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

A portion of the basis for these rejections is withdrawn. Specifically, the examiner no longer asserts that **mRNA levels** are not predictive of polypeptide levels. As a consequence, the Examiner is no longer relying on Haynes, Hu, Lilly or King for support of his position. The basis of the maintained rejections is solely that **gene amplification levels** are not predictive of mRNA or polypeptide levels.

In the interest of clarity, the basis of the maintained rejections is set forth here:

The claims are directed to the polypeptide of SEQ ID NO:326, wherein the polypeptide is amplified in colon cancer. It is noted that the claimed polypeptides recite the phrase "wherein the nucleic acid encoding said polypeptide is amplified in colon tumors." This is not an activity limitation for the claimed polypeptides; rather, it is a characteristic of a nucleic acid. In other words, the claims do not require that the polypeptides be overexpressed in any tumor, or have any biological activity. The specification discloses the polypeptide of SEQ ID NO: 326, also known as PRO1281. Applicants have gone on record as relying upon the gene amplification assay as providing utility and enablement for the claimed polypeptides. See Appeal Brief (received 2 July 2007), p. 4, (re:Example 170).

At pages 539-555 of the specification, Example 170 discloses a gene amplification assay in which genomic DNA encoding PRO1281 had a ΔCt value of at least 1.0 for two out of fourteen colon tumor samples when compared to a pooled control of blood DNA from several healthy volunteers. Example 170 asserts that gene amplification is associated with overexpression of the gene product (i.e., the polypeptide), indicating that the polypeptides are useful targets for therapeutic intervention in cancer and diagnostic determination of the presence of cancer (p. 539, lines 21-24). At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 1.29), and (b) that very few values were obtained that were at least 2.

First, there are several problems with the data provided in this example. Only two out of the fourteen colon cancer samples tested positive. Therefore, if a sample were taken from an individual with colong cancer for diagnosis, ***it is more likely than not that this assay would yield a false negative result.*** The gene amplification assay in the instant specification does not provide a comparison between the colon tumor samples and normal colon epithelium and does not correct for aneuploidy. Thus it is not clear that PRO1281 is amplified in cancerous colon epithelium more than in damaged (non-cancerous) colon epithelium. One skilled in the art would not conclude that PRO1281 is a diagnostic probe for colon cancer unless it is clear that PRO1281 is amplified to a clearly greater extent in true colon tumor tissue relative to non-cancerous colon epithelium.

Second, even if the data had been corrected for aneuploidy and a proper control had been used, and even if a majority of colon tumor samples had tested positive, the data have no bearing on the utility of the claimed PRO1281 *polypeptides*. In order for PRO1281 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO1281 mRNA or PRO1281 polypeptide levels in colon tumors have been brought forth on the record. The art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels. A specific example of the lack of correlation between genomic DNA amplification and increased mRNA expression is provided by Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and

> overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Another specific example is provided by Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract).

The *general* concept of gene amplification's lack of correlation with mRNA/protein overexpression in cancer tissue is addressed by Sen (2000, Curr. Opin. Oncol. 12:82-88). Specifically, Sen teaches that cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Again, the data in the specification were not corrected for such aneuploidy events.

Similarly, data pertaining to PRO1281 genomic DNA do not indicate anything significant regarding the claimed PRO1281 polypeptides. The data do not support the specification's assertion that PRO1281 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1281 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO1281 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO1281 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In view of the preponderance of evidence supporting the rejections (Pennica et al., Konopka et al., Sen, Godbout et al., and Li et al., all of which are of record and have been previously discussed), the

rejections are properly maintained.

Applicant's arguments pertaining to the remaining issues (Appeal Brief, 1 June 2007) have been fully considered but are not found to be persuasive for the following reasons.

Applicant's detailed arguments begin at p. 8 of the appeal brief. Applicant begins with a review of the legal standard for utility, with which the examiner takes no issue. However, the Examiner does believe that the conclusions of the case law cited by Appellants is not applicable here. Specifically, regarding Brenner, the Examiner believes that no "successful conclusion" has been reached. Regarding Nelson, the Court's statement that "tests evidencing pharmacological activity of a compound may establish practical utility" is also not pertinent in this case since, due to the fact that it is not "more certain than not" that the test provided in Example 170 of the instant specification demonstrate utility (i.e. pharmacological activity) as the art suggests otherwise. Furthermore, the Courts used the term "may." Therefore, even, *arguendo*, pharmacological activity were established, this may or may not provide for a practical utility. Similarly, with respect to Cross, the Court held that "*in vitro* results might be sufficient to support practical utility...Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results." Again, the Examiner argues that, due to the conflicting evidence in the art, the results are not sufficient to support a practical utility for the polypeptides of the instant invention and that the *in vitro* results are not predictive of *in vivo* results. Therefore, the Examiner believes he has established that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Appellants basically summarize their arguments on page 11 of the Brief by stating that "the Guidelines for Examination of Applications for Compliance With the Utility Requirement, gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." The Examiner's conclusion is that, based on a totality of the evidence in the art, the ordinarily skilled artisan would not find Appellants' assertion credible.

Beginning at p. 11 of the brief, Applicant reviews Example 170, and refers to the Goddard declaration as establishing that an amplification of at least 2-fold is significant and indicative of a cancer diagnostic marker. The Goddard declaration under 37 CFR 1.132 filed 22 July 2005 is insufficient to overcome the rejection of claims 119-121 and 123 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be

established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.099 to 2.219-fold amplification of the gene encoding PRO1281 in two colon tumors is significant. The significance can be questioned based on the absence of factual support for the expert's opinion. In the instant case, the facts are that twelve of the fourteen colon tumor samples did not show an amplification of the gene encoding PRO1281, and the control used was not a matched non-tumor colon sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). This art, as well as the Sen, Godbout et al., and Li et al. references cited above, constitute strong opposing evidence as to whether or not the claimed polypeptides have utility and enablement based on a presumption of overexpression in view of gene amplification data. Finally, while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues. Since the claims under examination are directed to polypeptides, not genes, this question is critical.

Applicant argues that the PRO1281 gene is an important diagnostic marker to identify malignant tumors even when the malignancy is a rare occurrence. Applicant urges that evidence has been provided that the PRO1281 polypeptide is significantly amplified in certain types of colon tumors and is therefore a valuable diagnostic marker for identifying certain types of colon carcinomas. This has been fully considered but is not found to be persuasive. First, respectfully, Applicant is incorrect with regard to the facts. It is important to clarify that no evidence has been brought forward to establish that the PRO1281 **polypeptide** is amplified in any colon tumors. The only evidence directly related to PRO1281 is found in Example 170 of the specification, which indicates that PRO1281 **gene** is amplified in twoe out of fourteen colon tumors as compared to a pooled blood DNA sample. Secondly, the PRO1281 gene was not amplified in twelve out of fourteen colon tumor samples, thus establishing that it is more likely than not that a colon sample from a patient suspected of having colon cancer will yield a false negative result in the disclosed assay. While it is true that markers for rare cancers are valuable, they are only valuable if the rare tumor is adequately described and distinguished from other tumors. Applicant stated in the arguments that PRO1281 is amplified in "malignant colon cancers." However, the specification and evidence of record do not establish which certain types these colon carcinomas are. Additionally, even if it could be established that PRO1281 gene is significantly amplified in colon carcinomas, it does not

follow that PRO1281 polypeptide would also be over-expressed and thus useful as a cancer diagnostic molecule, for reasons discussed extensively on the record.

Applicant points to the statement in Example 170 that gene amplification is associated with overexpression of the gene product, thus allegedly indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers and diagnostic determination of the presence of those cancers. This has been fully considered but is not found to be persuasive. Substantial evidence has been brought forth to establish that it is more likely than not that gene amplification is not associated with overexpression of the encoded protein.

Applicant relies on Orntoft et al., Hyman et al., and Pollack et al. as evidence that gene amplification increases mRNA expression in general. This has been fully considered but is not found to be persuasive. Applicant urges that Orntoft et al. looked at the correlation of mRNA levels and protein expression for individual genes. Applicant urges that Orntoft et al. find that there is a highly significant correlation between mRNA and protein alterations. Applicant argues that a correlation in 39 out of 40 gene examined supports their position that mRNA correlates with protein levels. This has been fully considered but is not found to be persuasive. First, the rejection is no longer based on the issue of whether or not mRNA levels are predictive of protein levels. Therefore, these findings of Orntoft et al. are no longer relevant to the rejection. Regarding the correlation of gene amplification with increased protein levels, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) Moreover, Orntoft et al. only concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO1281 in the instant specification. That is, it is not clear whether or not PRO1281 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al.'s results cannot be extended to the instant gene and protein.

Orntoft et al. used the CGH method to look at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. However, Orntoft et al. do not look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO1281 in the instant specification. That is, it is not clear whether or not PRO1281 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, Orntoft et al. does not support utility and enablement of the claimed polypeptides.

Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO1281 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

In discussing the utility of the polypeptides, Appellants argue the Examiner's citing of references like Pennica *et al* and, Konopka *et al.* to show that gene amplification data cannot reliably predict protein levels. Appellants have argued the references in great detail throughout prosecution, and have drawn the following conclusions -

> that even though certain instances where DNA/mRNA and protein levels do not correlate exist, in most cases, there is generally good correlation between DNA/mRNA and protein levels, and this was conclusively demonstrated in the more than 100 references submitted by the Appellants in the IDS filed August 2, 2006. The IDS included references that studied...gene amplification and microarray data.

However, the Examiner points out that there is no issue debated here as to whether or not mRNA levels are predictive of protein levels when these mRNA levels are identified via microarray.

Applicant refers to the Polakis declarations of 04 June 2004 and 2 August 2006. However, these are insufficient to overcome the rejection of claims 119-121 and 123 based upon 35 U.S.C. § 101 as set forth in the last Office action because the declarations focus on the question of whether or not mRNA levels are predictive of protein levels. As explained above, the examiner is no longer arguing this point. Since the Polakis declarations do not address the question of whether or not amplified genomic DNA is predictive of increased polypeptide levels, they are no longer considered pertinent to the rejection.

At the bottom of p. 18 of the brief, Applicant argues that over 100 references have been submitted to support the asserted utility. This has been fully considered but is not found to be persuasive, as it is now factually incorrect. The vast majority of these references speak to the question of whether or not mRNA levels are predictive of protein levels. As explained above, the examiner is no longer arguing this

point. Therefore, most of the references relied on by the Applicant are not longer relevant to the main basis of the rejections.

Applicant refers to the Ashkenazi declaration of 4 June 2004 as establishing that a polypeptide encoded by an amplified gene would still have utility even if the polypeptide itself were not overexpressed, because the absence of gene product overexpression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. While it may be true that lack of overexpression of a gene product can also provide useful information in tumor categorization, the specification does not disclose such further testing of PRO1281 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO1281 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1281. No evidence has been brought forth on the record as to whether or not PRO1281 polypeptide is overexpressed in colon tumors. Furthermore, the specification does not assert a utility for the claimed polypeptides based on the possibility that the PRO1281 polypeptide is not overexpressed in colon cancer tissue. Finally, the Ashkenazi declaration is viewed as supporting the instant rejections, since it contradicts the asserted utility in the specification at p. 539, lines 21-24:

> "Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, colon, breast and other cancers and diagnostic determination of the presence of those cancers."

Applicant next points to Hanna and Mornin (1999, Pathology Associates Medical Laboratories) as supporting the Ashkenazi declaration's rationale of utility for the claimed polypeptides. Applicant reasons that an assay relying on both gene amplification and protein expression tests leads to a more accurate classification of the cancer and a more effective treatment of it. This has been fully considered but is not found to be persuasive because Hanna and Mornin support the instant rejections. Hanna and Mornin provide another important example of a lack of correlation between gene amplification and mRNA/protein overexpression, wherein diagnosis of breast cancer included testing both the amplification of the HER-2/neu gene as well as over-expression of the HER-2/neu gene product. Thus Hanna and Mornin evidence that the level of protein expression must be tested empirically to determine whether or not the protein can be used as a diagnostic marker for a cancer. The specification does not provide data as to whether or not the protein level of PRO1281 was tested in normal and cancerous tissue, and thus the skilled artisan *must* perform additional experiments, as directed by the art. Since the asserted utility for

the claimed proteins is not in currently available form, and further experimentation is *required* to reasonably confirm the asserted real-world use, the asserted utility is not substantial. Regarding Applicant's argument that lack of protein overexpression leads to more effective categorization and treatments, the specification provides no assertion that the claimed PRO1281 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO1281. Therefore, significant further research would be required before such a utility were deemed substantial.

Applicants conclude that, based on the asserted utility for PRO1281 in the diagnosis of selected colon carcinomas, the reduction to practice of the PRO1281 protein sequence, the disclosure of methods for making polypeptides and chimeric polypeptides comprising PRO1281, and example 170 regarding the gene amplification assay, one skilled in the art would know exactly how to make and use the claimed polypeptides for diagnosis of colon carcinoma without undue experimentation. Applicant urges that, in general, DNA amplification correlates with increased expression of the encoded protein. Applicant argues that the specification shows significant amplification in three different colon primary tumors, evidence in the form of publications has been submitted to establish that a general DNA/mRNA/protein correlation exists, and declarations from experts have been provided to further support Applicant's position. Applicant concludes that the utility of the claimed PRO1281 polypeptides has been achieved. Applicant stresses that absolute certainty is not required, and that it has been established that it is more likely than not that PRO1281 polypeptides are overexpressed in certain colon tumors. This has been fully considered but is not found to be persuasive for the following reasons. Regarding the gene amplification assay itself, it is noted that PRO1281 gene was not amplified in twelve out of fourteen colon carcinoma samples. Therefore, PRO1281 it is more likely than not that a colon tumor sample will not have amplified PRO1281. Also, the assay did not correct for aneuploidy. Contrary to Applicant's assertion, the state of the art indicates that gene amplification is not generally associated with overexpression of the encoded gene product, as evidenced by Sen, Pennica et al., Konopka et al., Hanna and Mornin, Godbout et al., Hyman et al., and Li et al. Finally, a declaration setting forth the expert opinion of Dr. Ashkenazi contradicts the assertion of utility in the specification, wherein the specification indicates that gene amplification is associated with protein overexpression but Dr. Ashkenazi indicates that this is not always the case. Since significant further research would have been required of the skilled artisan to reasonably confirm that the claimed PRO1281 polypeptides are overexpressed in any cancer to the extent that they could be used as cancer diagnostic agents, the asserted utility is not substantial. In the absence of information regarding whether or not PRO1281 polypeptide levels are also different between specific

cancerous and normal tissues, the proposed use of the PRO1281 polypeptides as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

3. *Claim Rejections - 35 USC § 112, first paragraph - enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A. Claims 119-126 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 5 of the Office Action dated 9/6/06 as well as for the reasons given in the above rejection under 35 USC 101. Applicants argue that the claimed invention is enabled because it has utility as argued previously. Applicants' arguments have been fully considered, but are not found to be persuasive for the reasons discussed above.

B. Claims 119-123 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 5-6 of the Office Action mailed 8/30/06. In the Brief, Appellants argue that the claims recite structural features, namely, 80-99% sequence identity to SEQ ID NO: 326, which are common to the genus and that the genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in colon tumors. The also argue that the specification provides detailed guidance as to how to identify the recited variants of SEQ ID NO: 326, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence substitutions, as well as detailed protocols for determining whether a gene encoding a variant PRO1281 protein is amplified in

colon tumor and, therefore, one of skill in the art could easily identify whether a variant PRO1281 sequence falls within the parameters of the claimed invention, and would not view it as an "invitation to test" the invention. Accordingly, a description of the claimed genus has been achieved by the recitation of both structural and functional characteristics and one of ordinary skill in the art would understand how to make and use the recited polypeptide for the diagnosis of colon cancer without any undue experimentation.

These arguments have been considered, but are not deemed persuasive. Appellants have only identified one gene in the claimed genus. Given only this one gene, the ordinarily skilled artisan would not be able to determine identifying structural and functional characteristics which define the genus. While the specification provides guidance on how to identify variants with a certain percent identity and a protocol for determining such, this would still be an "invitation to test" since, again, the genus only has one working example. These arguments have been thoroughly discussed throughout prosecution.

It is believed that all pertinent arguments have been addressed.

4. *Claim Rejections - 35 USC § 112, first paragraph – written description*

A. Claims 119-123 and 129-131 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 6-7 of the Office Action mailed 8/30/06. In the Brief, Appellants argue case law regarding written description. The Examiner takes no issue with the case law. Appellants' arguments are essentially the same as above regarding enablement. The Examiner's rationale for maintaining the lack of written description rejection is also, therefore, the same. As with enablement, extensive arguments can be seen in every Office Action in the prosecution of this application. The bottom line is that Appellants have only identified one member of the genus. No structural limitations can reasonably be provided (other than that the protein is encoded by a nucleic acid overexpressed in a tumor) since the actual function of the proteins are not known. The artisan would not know to what family the proteins of this genus belong; therefore, the artisan would not know what residues are critical for protein function since there is no function.

It is believed that all pertinent arguments have been addressed.

5. Claim Rejections - 35 USC § 102

A. Claims 119-121 and 123 remain rejected under 35 USC 102 for the reasons already of record on page 7 of the Office Action mailed 8/30/07. In the Brief, Appellants argue that claims 119-121 and 123 should not be rejected under 35 USC 102(b) as being anticipated by Baker et al. since the instant invention has utility and, therefore, receives priority to June 23, 1999, which predates Baker et al. This argument has been considered, but is not deemed persuasive for the reasons discussed above in the rejection under 35 USC 101.

6. Conclusion

No claims are allowed.

No new rejections have been made, and no new evidence has been cited. THUS, THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman, Ph.D. whose telephone number is (571) 272-0888. The examiner can normally be reached on M-F 10 AM – 7 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao at 571-272-0835939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert Landsman, Ph.D.
Primary Examiner
Art Unit 1647